



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,468	08/31/2006	John S. Yu	67789-566	5815
50670 7590 05/19/2009 DAVIS WRIGHT TREMAINE LLP/Los Angeles 865 FIGUEROA STREET SUITE 2400 LOS ANGELES, CA 90017-2566				
EXAMINER				
MACFARLANE, STACEY NEE				
ART UNIT		PAPER NUMBER		
1649				
MAIL DATE		DELIVERY MODE		
05/19/2009		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/598,468

Applicant(s)

YU ET AL.

Examiner

STACEY MACFARLANE

Art Unit

1649

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) 4, 10, 11 and 13-33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-9, 12 and 34-39 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 31 August 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SF/08)
Paper No(s)/Mail Date 8/31/2006; 9/5/2007
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: ____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I and the species of A2B5 as the astrocytic marker, IL-12 as the heterologous gene and GBM as the disease or condition, in the reply filed on March 27, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants indicate claims 1-3, 5-9, 12 and 34-39 as reading upon the elected species.
2. Claims 4, 10, 11 and 13-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on March 27, 2009.
3. Claims 1-3, 5-9, 12 and 34-39, in so far as they read upon the elected species, will be examined upon their merits in the instant Office Action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2 and 5-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 2 recites "markers characteristic of a precursor for astrocytic differentiated stem cells". Claim 5 recites "a heterologous gene". Claims 6-8 depend from Claim 5 and do not further structurally limit the "heterologous gene" and are therefore included in the rejection. The claims do not require that the "markers" or "heterologous gene" possess any particular conserved structure or other distinguishing feature, thus, the claims are drawn to a genus of molecules that is defined merely defined by the function: for the markers the function being characterizing astrocyte precursors; for the heterologous gene, the function being that it encodes a polypeptide that is either cytotoxic or involved in immune response. The instant specification fails to describe the entire genera of molecules that are encompassed by these claims.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is not even clear that Applicant is in possession of specific examples of heterologous genes that encode therapeutic proteins that are cytotoxic and/or involved in immune response (paragraphs [0042] through [0044]). The claims encompass products comprising a broad genus of heterologous genes, thus, the claims are not limited to specific molecules with known structure. Furthermore, from the disclosure it is clear that Applicant is in possession of specific examples of markers that are characteristic of astrocyte precursor cells, namely GFAP and A2B5 (Figure 2). The claims, however, are

drawn to stem cell products exhibiting markers belonging to the genus of those characteristic for astrocytic precursor or differentiation. Therefore, the claims are not limited to specific molecules and the specification does not provide description for the entire genus encompassed.

In order to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure; physical and/or chemical properties; functional characteristics and structure/function correlation; methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claim is a recitation of functional activity. There is not even identification of any particular portion of the structure that must be conserved for said activity. As stated above, it is not even clear what molecules are encompassed by the claimed genera of markers and heterologous genes. The specification does not provide any structural description of either and fails to provide a representative number of species for the recited genera. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genera.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, the court clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the markers and genes encompassed by the claimed stem cell product, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of identifying molecules possessing said activity. Adequate written description requires more than a mere recitation of activity as part of the invention and a reference to a potential method of isolating or screening, the compound itself is required. See *Fiers v Revel*, 25 USPQ2d 1601 at 1601 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class because the specification only provided for the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-3, 5, 6, 12 and 34-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Lapidot et al. US Patent 7,101,708, filed July 20 1999, published February 10, 2000 and issued September 5, 2006, as evidenced by Kemshead et al., Int J Cancer, 27(4):447-452 (1981, abstract only).

Claims 1-3, 5, 6, 12 and 34-39 are drawn to an isolated stem cell which is isolated by a method comprising selecting the stem cell based on the cell exhibiting CXCR4 receptor, demonstrating an affinity for the chemokine SDF-1, or both; wherein said stem cell exhibits markers characteristic of astrocytic precursors; wherein said marker is A2B5; wherein the isolated stem cell comprises a heterologous gene; wherein the stem cell is a neural stem cell; and kits comprising said product and additional components for the treatment of disease conditions including the instantly-elected malignant glioblastoma multiforme.

Claims are directed to a product-by-process. Section 2113 of the MPEP states that Product-by-Process Claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. The courts have stated, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even

though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir.1985).

The Lapidot et al. prior art Patent teaches cell compositions consisting of hematopoietic CXCR4-positive progenitor and stem cells that are responsive to SDF-1. The Lapidot et al. Patent also explicitly teaches these cells wherein they express a heterologous gene for the treatment of disease, including malignancies (see for example, Column 9, lines 39-48 and Column 8, lines 58-67).

The Kemshead reference is relied upon as evidence that the "A2B5" marker is named after a monoclonal antibody that was directed against a cell surface ganglioside epitopes that can be found in hematopoietic leukemic marrow cells. Therefore, even though the Lapidot Patent does not explicitly teach their stem cell products as exhibiting A2B5 marker or as "neural stem cells", it can be argued that these are inherent features of the product-by-process. Thus, the product of the instant claims fails to distinguish over that of the prior art.

MPEP § 2112 provides guidance as to the Examiner's burden of proof for a rejection of claims under 35 U.S.C. 102 or 103 based upon the express, implicit, and inherent disclosures of a prior art reference. The case law clearly states that something which is old does not become patentable upon the discovery of a new property.

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Thus, the claiming of a new use, new function or unknown property that is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In addition the court has held that there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); *Abbott Labs v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999).

The case law specifically applies to the instant application where Applicant has claimed a composition in terms of a property or characteristic and the composition of the prior art is the same as that of the claim but the characteristic is not explicitly disclosed by the reference. In the instant case, Applicant's invention is directed to an isolated stem cell which exhibits CXCR4 receptor reactivity and demonstrates an affinity for SDF-1, and further exhibits the A2B5 ganglioside marker and is characterized as a "neural stem cell". The examiner has applied prior art which disclosed isolated stem cells which exhibit CXCR4 receptor reactivity and demonstrate an affinity for SDF-1. The examiner's assertion of inherency as to the A2B5 marker and the potential to

become a neural stem cell is based upon the structural similarity between the patented composition and the claimed composition.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established and the burden of proof rests upon the Applicant to demonstrate that the prior art does not necessarily or inherently possess the characteristics of Applicant's claimed product. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the product invention of the instant claims 1-3, 5, 6, 12 and 34-39 fails to distinguish over that of the prior art.

8. Claims 1-3, 5, 6, 12, 34-37 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Suda et al. US 2007/0053884 A1, filed May 14, 2009.

Claims 1-3, 5, 6, 12 and 34-39 are drawn to an isolated stem cell which is isolated by a method comprising selecting the stem cell based on the cell exhibiting CXCR4 receptor, demonstrating an affinity for the chemokine SDF-1, or both; wherein said stem cell exhibits markers characteristic of astrocytic precursors; wherein said marker is A2B5; wherein the isolated stem cell comprises a heterologous gene; wherein

the stem cell is a neural stem cell; and kits comprising said product and additional components for the treatment of disease conditions, including cancer.

The Suda et al. publication teaches isolated adult stem cells which are CXCR4-positive and reactive to SDF-1. The Suda reference teaches that said cells remain multi-potent with the ability to become neural stem cells, and contemplates their use in compositions for the treatment of diseases. While the reference does not explicitly teach does not explicitly teach stem cell products as exhibiting A2B5 marker, it can be argued that this is an inherent feature of the product-by-process. Thus, the product of the instant claims fails to distinguish over that of the prior art.

MPEP § 2112 provides guidance as to the Examiner's burden of proof for a rejection of claims under 35 U.S.C. 102 or 103 based upon the express, implicit, and inherent disclosures of a prior art reference. The case law clearly states that something which is old does not become patentable upon the discovery of a new property.

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Thus, the claiming of a new use, new function or unknown property that is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In addition the court has held that there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact

inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); *Abbott Labs v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999).

The case law specifically applies to the instant application where Applicant has claimed a composition in terms of a property or characteristic and the composition of the prior art is the same as that of the claim but the characteristic is not explicitly disclosed by the reference. In the instant case, Applicant's invention is directed to an isolated stem cell which exhibits CXCR4 receptor reactivity and demonstrates an affinity for SDF-1, and further exhibits the A2B5 ganglioside marker. The examiner has applied prior art which disclosed isolated stem cells which exhibit CXCR4 receptor reactivity and demonstrate an affinity for SDF-1, but does not explicitly indicate A2B5 ganglioside expression. The examiner's assertion of inherency as to the A2B5 marker is based upon the structural similarity between the patented composition and the claimed composition.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established and the burden of proof rests upon the Applicant to demonstrate that the

prior art does not necessarily or inherently possess the characteristics of Applicant's claimed product. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the product invention of the instant claims is rejected as failing to distinguish over that of the prior art publication.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidot et al. US Patent 7,101,708, as applied to claims 1-3, 5, 6, 12 and 34-39 above, and further in view of Tahara et al., Cancer Research, 54(1):182-189, 1994.

Claim 9 is drawn to an isolated stem cell selected for exhibiting CXCR4 and/or SDF-1 affinity and further comprising a heterologous gene encoding a polypeptide for the treatment of a disease condition involved in immune response, wherein said polypeptide is IL-12.

The Lapidot et al. prior art teaches cell compositions consisting of CXCR4-positive stem cells that are responsive to SDF-1 and for the expression of heterologous genes useful in the treatment of disease, including malignancies.

The Lapidot et al. art is silent with respect to heterologous genes encoding the specific polypeptide of IL-12, however, the Tahara et al. prior art teaches that it was well-known in the art that cells genetically engineered to secrete IL-12 can suppress tumor growth in vivo.

With respect to the claimed invention, the instant specification states that the stem cells of the invention "may be modified to express a heterologous gene encoding, for example, cytotoxic polypeptides involved in the treatment of cancer. For example ... cytokines including IL-12" [0042]. Therefore, the claim does not encompass a novel use of heterologous expression of IL-12 but merely builds upon that which was known in the art of cancer therapeutics.

In *KSR International Co. v. Teleflex, Inc.*, the Supreme Court has stated that combining prior art elements according to known method to yield predictable results is *prima facie* obvious if the following rationale can be applied:

- (1) the prior art includes each element claimed though not necessarily in the same reference.
- (2) it was within the technical grasp of one of ordinary skill in the art to combine the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately.
- (3) one of ordinary skill in the art would have recognized that the results of such combination were predictable.

(*KSR International Co. v. Teleflex, Inc.* 127 S. Ct. 1727, 82 USPQ2d 1385, Supreme Court, April 30, 2007).

One of ordinary skill in the art would recognize the use of heterologous IL-12 expression, as taught by Tahara et al., in combination with the stem cell for the treatment of cancer, as taught by the Lapidot et al. Patent. A skilled artisan would be motivated to combine the prior art elements because combination would result in effective compositions for the treatment of cancer. Based on the guidance and direction within the prior art, such combination would have been well within the technical grasp of a skilled artisan. Since each of the elements in combination are merely performing the same function as they did separately, then one of ordinary skill in the art would have been able to predictably combine the elements with a reasonable expectation of success. Therefore, the invention as a whole is *prima facie obvious*, if not actually anticipated by the reference.

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M-W and ALT F 5:30 to 3:30, TELEWORK-Thursdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/John D. Ulm/
Primary Examiner, Art Unit 1649